IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO: ALL ACTIONS**	**MDL No. 2243** Master Docket No. 3:08-cv-08 *Filed Electronically*

PLAINTIFFS' BRIEF OPPOSING PREEMPTION ON REMAND FROM THE SUPREME COURT

SEEGER WEISS LLP
55 Challenger Road
Ridgefield Park, NJ 07660

CARELLA, BYRNE, CECCHI, OLSTEIN, BRODY & AGNELLO, P.C.
5 Becker Farm Road
Roseland, NJ 07068

Plaintiffs' Co-Liaison Counsel

KELLOGG, HANSEN, TODD, FIGEL & FREDERICK, P.L.L.C.
1615 M Street, N.W., Suite 400
Washington, D.C. 20036

May 6, 2020

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page

CASES

CONSTITUTION, STATUTES, AND REGULATIONS

OTHER AUTHORITIES

INTRODUCTION

The Supreme Court's decision in this case clarified and narrowed the scope of preemption of pharmaceutical failure-to-warn claims, establishing requirements for preemption that Merck cannot satisfy. Preemption exists only when FDA has "prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1678 (2019). Because federal law generally *permits* manufacturers to add new warnings, failure-to-warn claims are "not ordinarily" preempted. *Id.* at 1679. To establish preemption, Merck must "show that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed [Merck] that the FDA would not approve changing the drug's label to include that warning." *Id.* at 1678. The "only agency actions" that can establish preemption are a regulation, a formal rejection of an adequate warning label, or another "agency action carrying the force of law." *Id.* at 1679.

This case meets none of the requisites for the preemption defense. FDA not only permitted but took the rare step of *mandating* the type of warning Plaintiffs contend was required by state law – namely, an adequate warning of atypical femoral fractures. Although Merck contends that FDA had previously rejected such a warning, the regulatory record refutes that contention. As the Supreme Court recognized, FDA's May 2009 Complete Response Letter "rejected Merck's proposal to warn of a risk of 'stress fractures.'" Stress fractures are "microscopic cracks." Atypical femoral fractures are very different; they are "complete breaks that cause great pain and require surgical intervention to repair." *Id.* at 1673, 1674. The Supreme Court also recognized that the FDA found the justification for Merck's stress-fracture proposal inadequate "because" of its misleading "[i]dentification of 'stress fractures.'" *Id.* at

1674. These conclusions, which flow from the Complete Response Letter's text and regulatory context, establish that FDA never prohibited Merck from warning of atypical femoral fractures. Furthermore, far from fully informing FDA of justifications for an atypical femoral fracture warning, Merck submitted a misleading explanation of the data that improperly conflated debilitating atypical femoral fractures with more common and minor stress fractures.

Merck's brief is an exercise in misdirection. Merck assumes, without ever demonstrating, that it proposed an adequate atypical femoral fracture warning, and it asserts that FDA rejected that warning based on insufficient scientific evidence that Fosamax causes atypical femoral fractures. But Merck ignores the Supreme Court's well-founded refutation of those premises based on the clear regulatory record. Similarly, Merck relies on Judge Pisano's vacated ruling and a legal brief filed by the U.S. Office of the Solicitor General, while disregarding the Supreme Court's rejection of their primary conclusions.

Merck gets one thing right, though for all the wrong reasons: "This case is not complicated." Merck Br. 30. Preemption requires a legally binding FDA rejection of a warning that would have been adequate under state law. Merck never provided an adequate atypical femoral fracture warning. It never informed FDA of the justifications for such a warning. And FDA never rejected such a warning. Therefore, Plaintiffs' claims are not preempted.

BACKGROUND

A. Under Federal Law, Drug Manufacturers Are Primarily Responsible For The Adequacy Of Their Warning Labels

Congress enacted the Federal Food, Drug, and Cosmetic Act ("FDCA") in 1938 to regulate (among other things) prescription drugs. *Wyeth v. Levine*, 555 U.S. 555, 574 (2009). Although the Act has been amended several times, Congress has never enacted an express

preemption provision relating to prescription drugs. Congress "determined that widely available state rights of action provided appropriate relief for injured consumers." *Id.*

Manufacturers must receive FDA approval to market a prescription drug. 21 U.S.C. § 355(a), (b)(1)(F). Federal law requires a manufacturer to update the label of an approved brand-name drug to warn of emerging risks. *See Merck*, 139 S. Ct. at 1677. FDA's changes being effected ("CBE") regulation expressly permits the manufacturer to make "[c]hanges in the labeling to reflect newly acquired information" without prior FDA approval, when the change is "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling." 21 C.F.R. § 314.70(c)(6)(iii)(A). A manufacturer also can apply for FDA approval to update the label through a "Prior Approval Supplement" ("PAS"), which (unlike a CBE) requires prior FDA approval. *Id.* § 314.70(b)(2)(v)(A).

FDA regulations establish the format of drug labeling. Two sections of the label are relevant here: "Adverse Reactions" and "Warnings and Precautions."[1] The Adverse Reactions section includes a listing of all "undesirable effect[s], reasonably associated with use of a drug." *Id.* § 201.57(c)(7). A manufacturer must list an adverse reaction if "there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." *Id.* The Warnings and Precautions section describes "clinically significant adverse reactions," "limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification)." *Id.* § 201.57(c)(6)(i). This section

[1] As noted by Merck (at 6 n.4), under older FDA regulations, the "Warnings" and "Precautions" sections were separate, so some underlying documents discuss the "Precautions" section. No party contends that the differences between the older and newer regulations for formatting of drug labels alter the preemption analysis.

"must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." *Id.*

If FDA "determines that [it] will not approve" either an application for a new drug or an application for a labeling supplement "in its present form," it will "send the applicant a complete response letter." *Id.* § 314.110(a). The complete response letter "will describe all of the specific deficiencies that the agency has identified in an application." *Id.* § 314.110(a)(1). FDA provides three options to an applicant who has received a complete response letter: (1) "[r]esubmit the application . . . , addressing all deficiencies identified in the complete response letter"; (2) "[w]ithdraw the application"; or (3) request a hearing at which FDA will make a final determination whether to approve or reject the application. *Id.* § 314.110(b).

Until the Food and Drug Administration Amendments Act of 2007 ("FDAAA"), FDA lacked authority to mandate that manufacturers change prescription drug labels. *See Wyeth*, 555 U.S. at 571. The FDAAA empowered FDA to initiate a process to mandate label changes if FDA "becomes aware of new safety information" that FDA "believes should be included in the labeling of the drug." 21 U.S.C. § 355(*o*)(4)(A) (Supp. III 2009). Congress included a "[r]ule of construction" that "[t]his paragraph shall not be construed to affect the responsibility of the [manufacturer] to maintain its label in accordance with existing requirements, including . . . [21 C.F.R. §] 314.70," *id.* § 355(*o*)(4)(I), which contains the CBE regulation described above.

B. Merck Failed To Take Steps Permitted Under Federal Law To Provide An Adequate Warning Of The Injury Suffered By Plaintiffs

Merck manufactures Fosamax, a brand-name osteoporosis drug that belongs to a class of drugs called bisphosphonates. *Merck*, 139 S. Ct. at 1673. Fosamax aims to preserve bone mass and prevent fractures by slowing down the body's natural process of breaking down bone, called

resorption. *Id.*; *see also* Ex. 1 at A1060. "However, the mechanism through which Fosamax decreases the risk of osteoporotic fractures may increase the risk of a different type of fracture." *Merck*, 139 S. Ct. at 1673. "[A]ll bones – healthy and osteoporotic alike – sometimes develop microscopic cracks" called "stress fractures" that "ordinarily heal on their own through the bone remodeling process." *Id.* By slowing down the body's natural breaking down of bone (resorption), Fosamax also slows down the body's normal buildup or repair of bone (formation). Ex. 1 at A1060. Because Fosamax disrupts the bone remodeling process, it "may cause stress fractures to progress to complete breaks that cause great pain and require surgical intervention to repair." *Merck*, 139 S. Ct. at 1674. These fractures are called "atypical femoral fracture[s]." *Id.*

An atypical femoral fracture ("AFF") is a debilitating fracture in which the thigh bone, or femur, breaks in two. Ex. 2 at A1148-49. Several features of atypical femoral fractures make them different from more common thigh fractures. They are low-energy fractures, meaning they are linked to no trauma or minimal trauma, and occur suddenly as the victim is going about a normal activity (e.g., stepping out of a car or opening a door). *Id.* at A1149. The fractures occur in a transverse or oblique pattern, meaning they cut across the bone, perpendicular to the femoral shaft, or slightly slanted. *Id.* They generally occur in the proximal (upper) third of the femoral shaft, or the subtrochanteric region, just below the two protuberances (called trochanters) at the top of the femur. *Id.* at A1148-49; *see* Addendum ("Add.") 8 (x-ray image of AFF).

The atypical femoral fractures suffered by Fosamax users are "much more significant than 'garden-variety' stress fractures." Ex. 3 at A884 (¶ 86). In a Supreme Court *amicus* brief, Dr. Joseph Lane (one of the world's foremost experts on atypical femoral fractures and a former Merck consultant) and Dr. Vincent Vigorita (an expert on pathology of bone disorders) elaborated on the difference between stress fractures and atypical femoral fractures. *See* Ex. 4,

Lane Decl. ¶¶ 1-2, 4 & Ex. 1 ("Lane/Vigorita Br.") at 7-16; Ex. 5, Vigorita Decl. ¶¶ 1, 3; *accord* Ex. 3 at A884 (¶ 86). While doctors generally treat stress fractures with "rest or inactivity," atypical femoral fractures often require "invasive surgery . . . involv[ing] the physician cutting through the patient's skin, fat, and muscle, and reaming out much of the cancellous bone in the medullary canal. A long rod is then hammered into place in order to reduce the fracture (or bring the bone fragments back into relative alignment). The rod is secured with bone screws." Ex. 4, Lane/Vigorita Br. 12, 13; *see also id.* at 14 (x-rays of AFFs repaired with rod and screws).

Fosamax's label did not mention a risk of femur fractures from its approval in 1995 through 2008. *See Merck*, 139 S. Ct. at 1674. But evidence accumulated over time that Fosamax causes atypical femoral fractures. *See generally* Pls.' Prelim. Statement of Facts at 5-35, MDL DN 2995-5 (Sept. 30, 2013) ("Fact Br.") (describing evidence). Leading orthopedic physicians recognized the connection early on. As early as 2002, they referred to atypical femoral fractures as "Fosamax Fractures" because those fractures were rare before Fosamax went on the market but became common in patients taking Fosamax. *See Merck*, 139 S. Ct. at 1674; Ex. 3 at A875-76 (¶ 52); Ex. 6 at A1261; Ex. 7 at A1254. In 2005, "Merck performed a statistical analysis of Fosamax adverse event reports, concluding that these reports revealed a statistically significant incidence of femur fractures." *Merck*, 139 S. Ct. at 1674; Ex. 8 at A1272-73; Ex. 9 at A1443. "And about the same time, Merck began to see numerous scholarly articles and case studies documenting possible connections between long-term Fosamax use and atypical femoral fractures." *Merck*, 139 S. Ct. at 1674; *see also In re Fosamax Prods. Liab. Litig.*, 852 F.3d 268, 275 (3d Cir. 2017).

In June 2008, an FDA project manager emailed Merck that FDA was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and

was "concerned about this developing safety signal." Ex. 10 at A1145. In September 2008, Merck submitted a PAS application, seeking FDA preapproval to amend the Adverse Reactions and Precautions sections of the Fosamax label. *Merck*, 139 S. Ct. at 1674; Add. 1 (proposed Precautions language); Ex. 11 at A2748-59 (excerpts of PAS submission). "In particular, Merck proposed adding a reference to 'low-energy femoral shaft fracture' in the Adverse Reactions section, and cross-referencing a longer discussion in the Precautions section that focused on the risk of stress fractures associated with Fosamax." *Merck*, 139 S. Ct at 1674. Every sentence after the first sentence of Merck's proposal characterized the thigh fractures at issue as "stress fractures." Add. 1. Merck's proposal never mentioned atypical femoral fractures. *See id.*

In April 2009, FDA project manager Karl Stiller emailed Merck concerning Merck's September 2008 PAS application. Stiller stated that FDA was prepared to approve language about femur fractures in the Adverse Reactions section; regarding the Warnings and Precautions section, he wanted to "work with [FDA's Office of Surveillance and Epidemiology] and Merck to decide on language for a W&P [Warnings and Precautions] atypical fracture language, if it is warranted." Ex. 12 at A1498.

On May 22, 2009, FDA sent Merck a Complete Response Letter in response to Merck's PAS application. Add. 2-3. As the Supreme Court explained:

> The FDA approved the addition to the Adverse Reactions section, but rejected Merck's proposal to warn of a risk of "stress fractures." The FDA explained that Merck's "justification" for the proposed change to the Precautions section was "inadequate," because "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." The FDA invited Merck to 'resubmit' its application and to "fully address all the deficiencies listed."

Merck, 139 S. Ct. at 1674 (citations omitted). Merck never voluntarily resubmitted its application. Nor did it ever exercise its option under the CBE regulation to provide a warning of atypical femoral fractures in the Precautions section of the Fosamax label.

The company engaged in informal communications with individual FDA employees. Stiller, the FDA project manager, called Merck's regulatory liaison James Adams the same day the Complete Response Letter was issued. According to Adams's notes of the call, Adams asked whether FDA was interested in "discuss[ing] what may be acceptable" for "the Precaution section," and Stiller indicated that Merck could pursue the matter through a "request[ ] . . . made formally through a submission to the file." Ex. 13, Confoy Decl. Ex. 69. In a June 2009 email to Stiller, Adams stated that Stiller had "recommend[ed]" in "a previous conversation" that if Merck wanted to have a meeting "to discuss the issues that were raised in the Complete response letter to Merck's proposed text for the Precautions section of the label," then "this meeting would be requested formally." Ex. 14, Ecklund Decl. Ex. 152. Days later, Stiller again called Adams. According to Adams's notes, Stiller again told Adams that Merck could "formally" request to have a meeting "to discuss language that the Division may deem appropriate for [the Precautions] section of the label." Ex. 15, Ecklund Decl. Ex. 154. In July 2009, Merck told FDA in a formal letter that a meeting request "will be submitted" to discuss "text for the Precaution section of the label concerning low-energy femoral shaft and subtrochanteric fractures." Ex. 16, Ecklund Decl. Ex. 153.

Despite assuring FDA that it would request a meeting to discuss femur fracture language for the Precautions section, Merck never did so. Ex. 17, Ecklund Decl. Ex. 119 (Adams Dep. 271:21-272:1). "Merck instead withdrew its [PAS] application and decided to make the changes to the Adverse Reactions section through the CBE process. Merck made no changes to the Precautions section at issue here." *Merck*, 139 S. Ct. at 1674 (citation omitted).

In March 2010, FDA issued a drug-safety communication stating that it was "working closely with outside experts," including a Task Force of the American Society for Bone and

Mineral Research ("ASBMR Task Force"), "to gather additional information that may provide more insight" into the connection between bisphosphonates and atypical femoral fractures. Ex. 18 at A1508. In September 2010, the ASBMR Task Force published a report describing the features of atypical femoral fractures, Ex. 2 at A1148-49, and concluding that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture," *id.* at A1167. The Task Force did not conduct any additional clinical research. Instead, it "review[ed]" the "currently available information" – all of which was available to Merck. Ex. 3 at A879 (¶ 62).

In October 2010, FDA announced it would require all bisphosphonate manufacturers to warn of atypical femoral fractures. Ex. 19 at A1118. FDA explained that the Task Force Report "summarized" existing "data," *id.* at A1119, and "helped [FDA] understand these fractures a little bit better," Ex. 20 at A1396, by "clarify[ing] the features of atypical femur fractures," *id.* at A1392. Merck proposed labeling language with five references to "stress fractures," including the language relating to risk factors for stress fractures that FDA had rejected in 2009. Ex. 21 at A1556-57. FDA struck out each reference to stress fractures and revised the language so that it was nearly identical to what FDA originally proposed. *Id.*; *compare* Ex. 22 at A1516-17 (initial FDA proposal). FDA explained that "the term 'stress fracture' was considered and was not accepted" because, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." Ex. 21 at A1540. "The label now refers to the fractures five times as 'atypical' without using the term 'stress fracture.'" *Merck*, 139 S. Ct. at 1675.

C. The District Court's Prior Dismissal Of Plaintiffs' Claims On Preemption Grounds Was Vacated On Appeal And Remanded For Further Consideration Under A Standard Articulated By The Supreme Court

Plaintiffs are Fosamax users who suffered atypical femoral fractures. Plaintiffs filed separate complaints against Merck, which were consolidated for pretrial administration in this MDL. Plaintiffs generally allege that they suffered atypical femoral fractures caused by their Fosamax usage and assert claims under state law for failure to warn, among other theories. As relevant here, Plaintiffs contend that Merck should have revised the Warnings and Precautions section of the Fosamax label to add an adequate warning of atypical femoral fractures.[2]

Although it is not Plaintiffs' burden under state law to articulate "a particular replacement warning," *Wyeth*, 555 U.S. at 565, Plaintiffs believe that Merck should have added a warning similar to the one FDA ultimately mandated in 2010. *See* Add. 5. Plaintiffs do not believe that the warning proposed by Merck in 2008 would have satisfied its state-law duty to warn because, among other things, that proposed warning was medically inaccurate and focused on stress fractures rather than atypical femoral fractures.

---

[2] Plaintiffs' failure-to-warn claims also encompass a theory that Merck should have warned earlier of atypical femoral fractures in the Adverse Reactions section of the label. The Third Circuit held that federal law does not preempt that theory and that the district court's grounds for granting summary judgment to Merck on the theory were erroneous. *See Fosamax*, 852 F.3d at 301-02. Merck did not seek Supreme Court review of those holdings. *See* Ex. 23, Merck Cert. Pet. 13 n.1. Merck thus properly acknowledges (at 13 n.6) that Plaintiffs' Adverse Reactions theory can go forward.

The Third Circuit also vacated the dismissal of Plaintiffs' claims other than failure to warn. *Fosamax*, 852 F.3d at 302. Merck did not seek certiorari review of that ruling. *See generally* Ex. 23, Merck Cert. Pet. (not mentioning non-failure-to-warn claims). Merck now attempts to resurrect its previous unsuccessful attempt to dismiss Plaintiffs' non-failure-to-warn claims through a half-sentence in the brief's conclusion (at 31). Merck forfeited that contention by failing to include any argument regarding the non-failure-to-warn claims in the body of its brief. In any event, Merck's preemption theory is inapplicable to these claims because they do not sound in failure to warn. *See* Pls.' Design & Other Non Failure to Warn Claim Br., MDL DN 2995-2 (Sept. 30, 2013).

The first bellwether trial involved the claims of Bernadette Glynn, who is no longer a plaintiff in the MDL. After a jury rejected Ms. Glynn's claims, finding that she had not suffered an atypical femoral fracture, Judge Pisano issued an unusual advisory opinion concluding that federal law preempted Ms. Glynn's claims. *In re Fosamax Prods. Liab. Litig.*, 951 F. Supp. 2d 695, 697, 701-05 (D.N.J. 2013) ("*Glynn*"). Through an order to show cause, Judge Pisano then applied the *Glynn* advisory opinion against all Plaintiffs and dismissed their claims as preempted. *See* Ex. 24 at A1-30. The Third Circuit vacated those dismissals and remanded, holding that Merck was not entitled to summary judgment on its preemption defense. *Fosamax*, 852 F.3d 268. The Supreme Court vacated the Third Circuit's judgment, clarified the legal standards regarding preemption, and remanded this case for reconsideration "to consider fully the standards we have described." *Merck*, 139 S. Ct. at 1680-81. The Third Circuit, in turn, remanded the case to this Court "to determine in the first instance whether the plaintiffs' state law claims are preempted by federal law under the standards described by the Supreme Court in its opinion." Order at 1, No. 14-1900 (3d Cir. Nov. 25, 2019) ("Remand Order").

Merck's retelling of the prior opinions (at 12-16) mischaracterizes and omits key aspects. In particular, Merck ignores the Third Circuit's and the Supreme Court's rejections of the principal conclusions underlying Judge Pisano's opinions. Judge Pisano concluded (1) that the warning FDA rejected in 2009 contained "the same language" that Plaintiffs contend would have been adequate under state law and (2) that "FDA did not reject the PAS due to Defendant's use of the phrase 'stress fracture,'" *Glynn*, 951 F. Supp. 2d at 704.

Contrary to Judge Pisano, the Third Circuit recognized that the Complete Response Letter did *not* reject the warning Plaintiffs contend state law required. The Third Circuit held that "the immediate 'legal' effect of the May 2009 letter, if any, was simply to reject Merck's

proposed warning." *Fosamax*, 852 F.3d at 293 n.135. The Third Circuit concluded that "[t]he question for preemption purposes is whether the FDA would have approved *a different label amendment* than the one it actually rejected in the May 2009 letter," and that the Complete Response Letter "does not answer" that question. *Id.* at 292-93 & n.135 (emphasis added). Despite recognizing that the FDA did not actually reject the type of warning Plaintiffs contend state law required, the Third Circuit held that Merck could obtain preemption if it could convince a jury by clear and convincing evidence that, in a "counterfactual world," the FDA "would have rejected" such a warning. *Id.* at 271, 274.

The Supreme Court likewise recognized that the Complete Response Letter did not reject an adequate warning of atypical femoral fractures. The Court explained that FDA "rejected Merck's *proposal to warn of a risk of 'stress fractures.'*" *Merck*, 139 S. Ct. at 1674 (emphasis added). The Supreme Court also rejected Judge Pisano's characterization of FDA's Complete Response Letter: that Letter "explained that Merck's 'justification' for the proposed change to the Precautions section was 'inadequate,' *because* '[i]dentification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature.'" *Id.* at 1674 (emphasis added).

In addition, the Supreme Court rejected the Third Circuit's premise that a manufacturer can show preemption by arguing that the FDA *would have* rejected a warning that it did not actually reject. The Court "elaborate[d] *Wyeth*'s requirements" and explained that preemption requires an affirmative showing that the FDA took "action[ ]" to "prohibit[ ] the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law." *Id.* at 1676, 1678. The Supreme Court also held that the question whether the FDA had taken such an action was for the court, not the jury. *Id.* at 1679-80.

ARGUMENT

I. A Failure-To-Warn Claim Is Not Preempted Unless FDA Issues A Fully Informed, Legally Binding Rejection Of A Warning Adequate Under State Law

Under the Supreme Court's decisions in *Wyeth v. Levine*, 555 U.S. 555 (2009), and *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019), a failure-to-warn claim against a brand-name drug manufacturer is not preempted unless FDA has actually rejected a warning adequate under state law in a formal, legally binding action after being fully informed about the justifications for that warning.

The constitutional source of preemption doctrine is the Supremacy Clause. *Merck*, 139 S. Ct. at 1679 (quoting U.S. Const. art. VI, cl. 2). Congress can preempt state law either expressly or impliedly. Congress has never enacted an express preemption provision covering prescription drugs. *See Wyeth*, 555 U.S. at 574.

Merck has argued for just one form of implied preemption here, impossibility preemption. "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011). As *Wyeth* explained, for failure-to-warn claims against brand name drug manufacturers, the answer to that question is yes: a brand-name drug manufacturer not only has the right under the CBE regulation to update drug labels to strengthen warnings on account of new safety information without "wait[ing] for FDA approval"; it has the "responsibility" to "ensure[ ] that its warnings remain adequate." 555 U.S. at 568, 570-71. As explained in *Merck*, "the CBE regulation permits changes [to warning labels], so a drug manufacturer will *not* ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." 139 S. Ct. at 1679 (emphasis added).

Wyeth allowed only a narrow exception to its rule that failure-to-warn claims against brand-name manufacturers are not preempted: because "FDA retains authority to reject labeling changes made pursuant to the CBE regulation," a manufacturer could mount a preemption defense by providing "clear evidence that the FDA would not have approved a change to [the drug]'s label." 555 U.S. at 571. Some courts had understood *Wyeth* to permit preemption on a showing that, *if* the manufacturer *had* proposed an adequate warning, FDA would have rejected it. For example, the Third Circuit reasoned that "[t]he question for preemption purposes is whether the FDA would have approved a different label amendment than the one it actually rejected in the May 2009 letter," describing this question as, "in a counterfactual setting, what do you think the FDA would have done?" *Fosamax*, 852 F.3d at 292-93.

In *Merck*, the Supreme Court "elaborate[d] on *Wyeth*'s requirements" and rejected the theory of counterfactual preemption that the Third Circuit had initially recognized. 139 S. Ct. at 1676. The Supreme Court "h[e]ld" that, to establish preemption, a manufacturer "must show" that "federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law." *Id.* at 1672, 1678. To meet that burden, the manufacturer must "show that it fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Id.* at 1678. Anything less is insufficient because the Court has "cautioned many times before" that "the 'possibility of impossibility [is] not enough.'" *Id.* (quoting *Mensing*, 564 U.S. at 625 n.8) (alteration in original).

The Court further rebuffed arguments advanced by many defendants (including Merck) that they could establish preemption by arguing that the FDA conveyed disapproval of a warning

through informal, non-binding communications. As the Court explained: "the only agency actions that can determine the answer to the pre-emption question, of course, are agency actions taken pursuant to the FDA's congressionally delegated authority." FDA may "communicate its disapproval of a warning by means of notice-and-comment rulemaking setting forth labeling standards; by formally rejecting a warning label that would have been adequate under state law; or with other agency action carrying the force of law." *Id.* at 1679 (citations omitted).

Merck mischaracterizes the Court's opinion when it contends (at 28-30) that the Supreme Court merely "gave a non-exhaustive list" of FDA actions that can establish preemption and that Merck can still argue for preemption based on informal FDA communications such as phone calls between Merck and FDA officials. The Supreme Court gave two examples of legally binding actions, and then stated that FDA could preempt state law through "*other* agency action *carrying the force of law*." Thus, only agency actions carrying the force of law can have preemptive effect. That is because "the Supremacy Clause grants 'supreme' status only to the 'the *Laws* of the United States,'" *Merck*, 139 S. Ct. at 1679 (quoting U.S. Const. art. VI, cl. 2), and nonbinding agency actions are not "Laws of the United States."

The Third Circuit recently rejected Merck's interpretation of the Supreme Court's opinion, holding that a drug manufacturer "cannot rely on its informal phone conversations with an FDA official to claim that it could not pursue a label change through the CBE process," because "[a]n informal phone conversation with an FDA official is not an 'agency action taken pursuant to the FDA's congressionally delegated authority.'" *In re Avandia Mktg., Sales & Prods. Liab. Litig.*, 945 F.3d 749, 760 (3d Cir. 2019) (quoting *Merck*, 139 S. Ct. at 1679). Under *Merck* and *Avandia*, only an FDA rejection carrying the force of law can support preemption.

II. FDA Did Not Reject An Adequate Warning Of Atypical Femoral Fractures

Merck cannot establish preemption because FDA never rejected an adequate warning of atypical femoral fractures. As the Supreme Court explained, FDA can "communicate its disapproval" of a warning required by state law in three ways: (1) "notice-and-comment rulemaking setting forth labeling standards"; (2) "by formally rejecting a warning label that would have been adequate under state law"; (3) or "with other agency action carrying the force of law." *Merck*, 139 S. Ct. at 1679. FDA did not engage in any of those actions. Merck has never contended that FDA enacted a notice-and-comment rule (option 1) or took "other . . . action carrying the force of law" that prevented Merck from warning of atypical femoral fractures (option 3).

Nor did FDA "formally reject[ ] a warning label *that would have been adequate under state law*" (option 2). The only warning label FDA rejected was "Merck's proposal to warn of a risk of 'stress fractures.'" *Id.* at 1674. That warning was *inadequate* because it contained medically inaccurate information and did not describe the atypical femoral fractures at issue. As the Supreme Court explained, the FDA found Merck's justification for its stress-fracture proposal lacking "*because* '[i]dentification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature.'" *Id.* (emphasis added). Merck seeks here (at 26) to defy the Supreme Court by contending that FDA rejected the scientific link between Fosamax and atypical femoral fractures. But the Complete Response Letter contains no such language.

Because FDA never rejected an adequate warning of atypical femoral fractures, Merck asks this Court to draw speculative inferences based on informal FDA communications that FDA would have rejected such a warning if Merck had proposed it. That is exactly the kind of

counterfactual preemption the Supreme Court foreclosed. Straightforward application of the Supreme Court's decision compels rejection of Merck's preemption defense.

A. Merck Never Proposed An Adequate Warning Of Atypical Femoral Fractures

Merck's preemption defense requires it to show that the FDA took "action[ ]" to "prohibit[ ] [Merck] from adding any and all warnings to the drug label that would satisfy state law." *Merck*, 139 S. Ct. at 1678. To show that FDA *prohibited* an adequate warning of atypical femoral fractures, Merck first must establish that it *proposed* such a warning.

Merck's brief assumes, without ever demonstrating, that the proposed warning FDA rejected is substantively no different from the adequate warning of atypical femoral fractures that Plaintiffs contend state law required. *See, e.g.*, Merck Br. 1 (characterizing Merck's proposal as a "proposed warning about atypical fractures"); *id.* at 21. Not only is Merck incorrect, but the Supreme Court has already rejected Merck's premise. The Court recognized that Merck's proposed warning "focused on the risk of stress fractures," which are "microscopic cracks" that "ordinarily heal on their own," whereas atypical femoral fractures are "complete breaks that cause great pain and require surgical intervention to repair." *Merck*, 139 S. Ct. at 1673-74.

The text of Merck's proposed warning (quoted in full in the addendum) confirms the focus on stress fractures, not atypical femoral fractures. Every sentence after the first sentence described the fractures as "stress fractures." *See* Add. 1.[3] "There was no mention in Merck's proposed warning of atypical femoral fractures." Ex. 25, Sharfstein Br. 4-5.

X-ray images starkly illustrate the differences between the "stress fractures" about which Merck proposed to warn and the atypical femoral fractures suffered by Plaintiffs. The image of a

[3] The first sentence referred to "low-energy femoral shaft fracture," which is "a broad category that includes AFFs and less serious fractures." Ex. 25, Sharfstein Decl. ¶ 3 & Ex. 1 ("Sharfstein Br.") at 4.

stress fracture of the femur shows a fracture that is barely perceptible. Add. 7. The images of atypical femoral fractures show a gruesome injury in which the thigh bone (the largest and strongest bone in the body) looks like a pencil snapped in two. Add. 8. A warning of the risk portrayed in the first image is not an adequate warning of the risk displayed in the other images.

Merck's proposed warning threatened to mislead physicians about the nature of the relevant risk. While "[t]he term 'stress fracture' conveys to the prescriber a fracture which typically can be treated conservatively . . . by prescribing rest or inactivity," atypical femoral fractures "require invasive surgery." Ex. 4, Lane/Vigorita Br. 12, 13. Merck's proposal "failed to convey" the "unique features" of atypical femoral fractures, instead incorrectly stating that the fractures "had 'similar clinical features' to fractures suffered by non-bisphosphonate patients." *Id.* at 16. Merck's proposed language "would not have conveyed to physicians and patients" that "Fosamax patients were experiencing serious fractures that orthopedic physicians had not previously seen." *Id.* at 7. Dr. Lane explained to Merck – while Merck was preparing its warning – that atypical femoral fractures "should not have been characterized as stress fractures." *Id.* at 18; *see also* Ex. 26 at A1341-42 (Merck minutes of meeting with Dr. Lane and other consultants).

Merck belatedly acknowledged that its proposed focus on stress fractures would confuse "general physicians who prescribe the great majority of bisphosphonates." Ex. 27 at A1573. It admitted in a December 2010 internal email "that most of the stress fractures general physicians have seen are associated with repetitive stress injury related to exercise (e.g., running) in younger adults, and that this type of stress fracture generally heals well with rest." *Id.*

Because Merck's stress-fracture proposal was not an adequate warning of atypical femoral fractures, it follows that FDA's letter addressing that proposal did not reject an adequate

warning of atypical femoral fractures. As explained in a Supreme Court *amicus* brief by Dr. Joshua Sharfstein, FDA's number two official in charge of labeling when FDA responded to the PAS, *see* Ex. 25, Sharfstein Decl. ¶ 1, "FDA rejected Merck's request to add a Warning about stress fractures. It could not and did not reject a warning regarding AFFs, because Merck had never asked for one." *Id.*, Sharfstein Br. 12. Justice Kagan made a similar point through a hypothetical posed at oral argument: equating a warning focused on stress fractures to an adequate warning of atypical femoral fractures is like saying that a warning about readily treatable ovarian cysts constitutes an adequate warning of deadly ovarian cancer. Ex. 28, Oral Arg. Tr. 4:8-5:12.

B. The Complete Response Letter Did Not Prevent Merck From Adding An Adequate Warning Of Atypical Femoral Fractures

Because Merck never proposed "a warning that would satisfy state law," *Merck*, 139 S. Ct. at 1678 – meaning an adequate warning of atypical femoral fractures – Merck cannot show that FDA ever prohibited Merck from adding that warning. The text of FDA's Complete Response Letter and the regulatory context confirm that conclusion. Merck's contention that preemption applies because FDA did not mandate a warning sooner lacks merit.

1. The text of the Complete Response Letter confirms that FDA rejected Merck's stress-fracture proposal, but did not reject an adequate warning of atypical femoral fractures. The first sentence of FDA's explanation for rejecting the stress-fracture warning states that "[Merck's] justification for the proposed **PRECAUTIONS** section language is inadequate." Add. 2. FDA limited its criticism to Merck's "proposed . . . language" regarding stress fractures, not to warnings of atypical femoral fractures. The next sentence explains that the justification for Merck's warning was inadequate because "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature."

Id. FDA's critique was not that the "literature" contained insufficient evidence that Fosamax causes atypical femoral fractures; it was that Merck's discussion of "stress fractures" misidentified the risk shown by the literature. Next, FDA explained that "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting." Add. 2-3. Again, FDA did not state that the "available literature" or "post-marketing adverse event reporting" revealed no relationship between Fosamax and atypical femoral fractures. Rather, what was "not adequately supported" was "[d]iscussion of the risk factors for stress fractures." A warning listing risk factors unrelated to atypical femoral fractures would confuse physicians and patients and make it less likely they would recognize an atypical femoral fracture.

Nowhere in the Complete Response Letter did FDA mention what Merck now argues was the real reason for FDA's rejection of its application: the supposed lack of causal evidence connecting Fosamax to atypical femoral fractures. That omission is dispositive because the applicable regulation requires FDA to "describe all of the specific deficiencies that the agency has identified in [the] application," 21 C.F.R. § 314.110(a)(1), an important requirement so that the applicant can determine whether it can remedy those deficiencies by submitting a revised application. Interpreting the Complete Response Letter as a rejection on scientific grounds of an atypical femoral fracture warning would thus require accepting the premise that the FDA wrote a false Complete Response Letter that – in contravention of its regulatory duties – omitted the real reason for the FDA's decision.

Merck advances an atextual reading of the Complete Response Letter, attempting to conjure a scientific rejection of atypical femoral fracture warnings that does not appear in the letter. Merck characterizes the first sentence – "your justification for the proposed

PRECAUTIONS section language is inadequate," Add. 2 – as "a commentary on the absence of a sufficiently clear link between Fosamax and the atypical fractures at issue." Merck Br. 26. Of course, the FDA's actual letter does not discuss evidence of causation of atypical femoral fractures; that "commentary" is wholly invented by Merck.

As with many of Merck's arguments, the Supreme Court has already rejected Merck's reading of the Complete Response Letter. The Supreme Court interpreted the Complete Response Letter as follows: "The FDA explained that Merck's 'justification' for the proposed change to the Precautions section was 'inadequate,' *because* '[i]dentification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature.'" *Merck*, 139 S. Ct. at 1674 (emphasis added). The sentence identifying Merck's "justification" as "inadequate" was not, as Merck contends, a veiled rejection of any connection between Fosamax and atypical femoral fractures. It was an introduction, followed by two subsequent sentences explaining that the justification for Merck's proposed language was inadequate *because* Merck had not shown that its stress-fracture language accurately described the atypical femoral fractures in the literature.

Moreover, Merck's litigation position is the opposite of its contemporaneous reading of the Complete Response Letter. The day Merck received the letter, Merck's Director of Clinical Research Arthur Santora interpreted it to convey that "FDA wouldn't let us mention stress fractures." Ex. 29 at A1506. That same day, Merck's U.S. Regulatory Liaison James Adams informed his colleagues that FDA "believes that 'stress fractures' may not be clearly related to atypical subtrochanteric fractures." Ex. 30 at A1504. Adams testified under oath that the Complete Response Letter "doesn't make any mention of" any "belie[f] there was insufficient evidence to establish a causal association between Fosamax and atypical femur fractures." Ex.

17, Ecklund Decl. Ex. 119 (Adams Dep. 265:12-18). Merck's scientists correctly interpreted FDA's Complete Response Letter; its lawyers have not.

Given the Supreme Court's rejection of Merck's interpretation, it matters not a whit that the Office of the Solicitor General ("OSG") offered a legal interpretation of the Complete Response Letter similar to Merck's interpretation. *See* Ex. 31, U.S. Merits Amicus Br. 31. A court does "not defer[ ] to an agency's *conclusion* that state law is pre-empted." *Wyeth*, 555 U.S. at 576 (rejecting reliance on prior decision that Merck cites (at 23, 25)). Moreover, OSG's interpretation is illogical and divorced from the Letter's text for the reasons described above. The Supreme Court gave no weight to OSG's briefs when it rejected OSG's interpretation and instead correctly recognized that FDA found Merck's justification for its stress-fracture proposal inadequate *because* of the focus on stress fractures.

In any event, Merck overstates the import of OSG's briefs. The briefs are not, as Merck contends (at 25), factual "evidence" of what the FDA did in 2009 and 2010. They are legal interpretations of the Complete Response Letter submitted by government lawyers under a subsequent administration, nearly a decade after the fact. *See*, *e.g.*, Ex. 32, U.S. Cert. Amicus Br. 19 (describing interpretation of the Complete Response Letter as OSG's "conclusion," purportedly based on its reading of the letter and other regulatory context). To the extent that the Court finds the perspective of regulatory personnel instructive, the relevant brief is the one submitted by Dr. Sharfstein, the FDA official who oversaw drug labeling during the relevant period. As Dr. Sharfstein explained: "FDA rejected Merck's request to add a Warning about stress fractures. It could not and did not reject a warning regarding AFFs, because Merck had never asked for one. Nothing in the Complete Response Letter supports what Merck and the Solicitor General contend was the reason behind FDA's decision: a finding by FDA that there

was a lack of scientific evidence that Fosamax caused atypical femoral fractures." Ex. 25, Sharfstein Br. 12. The Supreme Court rejected Merck's revisionist history, and Merck offers no basis for this Court to reach a different conclusion.

Equally baseless is Merck's suggestion (at 17, 24) that this Court should blindly adopt Judge Pisano's conclusion that FDA "did not reject the PAS due to Defendant's use of the phrase 'stress fracture,'" and "simply reinstate" his preemption holding. As explained above, *see supra* pp. 11-12, the Third Circuit and Supreme Court rejected the key conclusions on which Judge Pisano's opinions were based. Furthermore, the Supreme Court made clear that it was necessary to reconsider preemption afresh because the lower courts "did not have an opportunity to consider fully the standards we have described." *Merck*, 139 S. Ct. at 1680. The Third Circuit further instructed this Court "to determine in the first instance whether the plaintiffs' state law claims are preempted by federal law under the standards described by the Supreme Court in its opinion." Remand Order at 1. If either the Supreme Court or the Third Circuit believed that Judge Pisano's ruling fully and accurately applied the standards articulated by the Supreme Court, they could have "simply reinstated" his ruling, but they did not do so. In asking this Court for that result, Merck invites defiance of the higher courts' remand orders.

2. Regulatory context provides additional evidence that the Complete Response Letter did not render compliance with state law impossible. A complete response letter provisionally rejects an application "in its present form," subject to the applicant's ability to win approval if it corrects "the specific deficiencies" described in the letter. 21 C.F.R. § 314.110(a)(1). The letter's purpose is "to inform[ ] sponsors of changes that must be made before an application can be approved, with *no implication as to the ultimate approvability of the application*." 73 Fed. Reg. 39,588, 39,589 (July 10, 2008) (emphasis added). Under the

regulation, Merck could have "[r]esubmit[ted] the application" with an accurate discussion of atypical femoral fractures that "address[ed]" the "deficiencies" in Merck's stress-fracture proposal "identified in the complete response letter." 21 C.F.R. § 314.110(b). Because a complete response letter is "merely tentative or interlocutory," it is best viewed as "not a final agency action with the force of law," and therefore not " 'Law' with pre-emptive effect." *Merck*, 139 S. Ct. at 1683 (Thomas, J., concurring).

Even assuming, for the sake of argument, that a complete response letter could in some cases support preemption, in this case, the Complete Response Letter addressed only Merck's stress-fracture proposal. *See* 21 C.F.R. § 314.110(a)(1) (complete response letter addresses manufacturer's application "in its present form"). The Third Circuit correctly recognized that "the immediate 'legal' effect of the May 2009 letter, if any, was simply to reject Merck's proposed warning," which "d[id] not answer the larger question of whether the FDA would have approved a differently-worded warning." *Fosamax*, 852 F.3d at 293 n.135.[4]

3. Merck argues that, because FDA did not mandate in the Complete Response Letter that Merck add a corrected atypical femoral fracture warning, one can infer that FDA would have rejected any atypical femoral fracture warning. Merck Br. 25. This argument rehashes a theory the Supreme Court rejected in *Wyeth* and *Merck*, that a manufacturer's state-law duty to add adequate warnings is preempted unless and until FDA mandates a label change.

[4] In *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803 (7th Cir. 2018), cited by Merck (at 27), the Seventh Circuit perceived no difference in the warning rejected by FDA and the warning sought by the plaintiff. *See Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882, 885 (7th Cir. 2020) (plaintiff argued that "GSK had negligently omitted an adult suicide risk on the drug label"; "GSK attempted . . . to add an adult suicide warning," and "FDA rejected that change"). Speculation that "GSK might have been able to persuade the FDA to change its mind in a formal meeting" was insufficient to avoid preemption. 901 F.3d at 814. This case is different because Merck never provided, and FDA never rejected, an adequate warning of atypical femoral fractures. *See Merck*, 139 S. Ct. at 1674 (Merck proposed warning of "stress fractures").

In *Wyeth*, the Court explained that, "[w]hen Congress granted the FDA th[e] authority" to mandate label changes, "it reaffirmed the manufacturer's obligations and referred specifically to the CBE regulation, which both reflects the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval." 555 U.S. at 571; *see also* 21 U.S.C. 355(*o*)(4)(I). Thus, when new safety information regarding a risk arises, the manufacturer "ha[s] a duty to provide a warning that adequately describe[s] that risk, and the CBE regulation permit[s] it to provide such a warning before receiving the FDA's approval." *Wyeth*, 555 U.S. at 571. In *Merck*, the Supreme Court clarified that preemption requires FDA "action" that "prohibited" an adequate warning that would comply with state law. 139 S. Ct. at 1678. FDA inaction is insufficient. Supreme Court precedent thus precludes Merck's attempt to avoid liability based on the FDA's supposed failure to mandate a warning.

Merck's account also ignores the full context of what FDA told Merck. Merck reasons (at 28) that, if any atypical femoral fracture warning were scientifically justified, FDA simply would have "propose[d] a redline" to Merck's stress-fracture proposal. But FDA told Merck that it was not sure precisely what an accurate atypical femoral fracture would look like, and that it needed Merck's help to figure that out. *See* Ex. 12 at A1498 (FDA wanted to "work with" Merck "to decide on language" for a warning). Merck's "attempt[ ] to confound the true nature of the association between Fosamax and AFFs," Ex. 3 at A883 (¶ 81), through a misleading PAS submission that "obfuscate[d] the true nature of AFFs," Ex. 25, Sharfstein Br. 22, likely contributed to FDA's need for help. *See infra* pp. 33-34. The deficiencies in Merck's inaccurate proposed warning were neither "editorial," 21 C.F.R. § 314.105(b), nor "easily correctable," *id.* § 314.102(b), so the regulations cited by Merck (at 7) stating that the FDA itself will correct such deficiencies are inapplicable.

Merck erroneously suggests it would have been "dereliction" for FDA not to immediately require a warning if one was scientifically justified, akin to "leaving patients to suffer in the dark." Merck Br. 14, 25. That assertion ignores that FDA repeatedly asked Merck to engage further on an atypical femoral fracture warning. *See supra* pp. 7-8; *infra* p. 33. Merck initially promised to work with FDA on an atypical femoral fracture warning, then inexplicably failed to follow through. *See supra* p. 8; *infra* p. 33. The "dereliction" was Merck's, not FDA's, and Plaintiffs are the patients who have "suffer[ed] in the dark" because of it.

Moreover, FDA's reliance on Merck to help it "decide on" the language of an appropriate atypical femoral fracture warning was reasonable and consistent with normal FDA practice. After all, the FDCA and FDA regulations impose on each brand-name drug manufacturer the "responsibility" to "ensur[e] that its warnings remain adequate as long as the drug is on the market." *Wyeth*, 555 U.S. at 570-71. That is in large part because even though FDA gained authority in 2008 to mandate label changes, it still "has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." *Id.* at 578-79 (footnote omitted). As Sen. Ted Kennedy explained in his statement regarding the FDAAA's enactment, Merck's annual sales of Fosamax Plus D "alone exceed[ed] the entire $120 million FDA budget for drug safety." 153 Cong. Rec. S11,831, S11,832 (daily ed. Sept. 20, 2007).[5] FDA's reliance on

[5] It is therefore unsurprising that post-FDAAA passage, FDA continued to rely primarily on manufacturers to initiate label changes. In the two years following the FDAAA's enactment (through Sept. 2009), FDA required safety-related labeling changes just 22 times, but in a partially overlapping two-year period (2009 and 2010), drug manufacturers submitted 363 CBE supplements for the same type of change. *See* FDA, *FDAAA Implementation – Highlights Two Years After Enactment*, http://tiny.cc/6z9gnz; FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products* 7, https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm375128.pdf.

Merck's expertise and superior resources in crafting an appropriate warning does not absolve Merck of its federal responsibility, or its duty under state law, to maintain adequate warnings.

C. The Full Context Of FDA's Communications Refutes Merck's Preemption Defense

Merck relies on a barrage of informal FDA communications (such as phone calls between FDA officials and Merck employees) to support its preemption defense, arguing that these informal communications show that FDA would have rejected any atypical femoral fracture warning before September 2010. That reliance fails for two reasons.

First, the Supreme Court's decision forecloses Merck's arguments. Preemption requires showing that FDA actions "prohibited" Merck from adding a warning that "would satisfy state law," and "the only agency actions that can determine the answer to the pre-emption question, of course, are agency actions taken pursuant to the FDA's congressionally delegated authority." *Merck*, 139 S. Ct. at 1678, 1679. Thus, Merck "cannot rely on its informal phone conversations with an FDA official," because such informal communications are "not an 'agency action taken pursuant to the FDA's congressionally delegated authority.'" *Avandia*, 945 F.3d at 760 (quoting *Merck*, 139 S. Ct. at 1679). Those informal statements also do not "carry[ ] the force of law" and therefore cannot "determine the answer to the pre-emption question." 139 S. Ct. at 1679.

Merck aims to get around *Merck*'s and *Avandia*'s bar on relying on informal FDA communications as a basis for preemption by arguing (at 30) that informal FDA communications "can be used merely to shed light on the meaning of the CRL." But even if such use of informal communications were legally permissible – and the Third Circuit's flat statement that manufacturers "cannot rely on" such communications confirms it is not – Merck does not use informal communications to shed light on the Complete Response Letter's meaning, but to conjure a basis for preemption that is not found in the Complete Response Letter's text. Merck

argues (at 21) that the informal communications show that FDA "was not prepared to approve an atypical-fracture warning," but the Complete Response Letter itself contains no rejection of an atypical femoral fracture warning. *See supra* pp. 20-21. Although Merck "argu[es], based on various agency communications, . . . that the FDA would have rejected a hypothetical labeling change submitted via the CBE process," *Merck*, 139 S. Ct. at 1682 (Thomas, J., concurring), that argument only underscores that the Complete Response Letter did not itself "communicate FDA's disapproval" of such an atypical femoral fracture warning, *id.* at 1679 (majority opinion).[6] Unfortunately for Merck, "neither agency musings nor hypothetical future rejections constitute pre-emptive 'Laws' under the Supremacy Clause." *Id.* at 1682 (Thomas, J., concurring); *accord id.* at 1678 (majority opinion) (preemption requires "action[ ]" that "prohibited" Merck from adding an adequate warning).

Second, Merck's reliance on informal FDA communications mischaracterizes the record. FDA employees told Merck in informal communications both before and after sending the Complete Response Letter that they welcomed further engagement with Merck regarding Warnings and Precautions language on atypical femoral fractures – not that Merck was prohibited from providing such a warning. In April 2009, the month before the Complete Response Letter, an FDA regulatory project manager wrote Merck and said it wanted to "work with . . . Merck to decide on language for a [Warnings and Precautions] atypical fracture language, if it is warranted." Ex. 12 at A1498. "[T]his email was an invitation to Merck to work with FDA to agree on language that warned about AFFs." Ex. 25, Sharfstein Br. 13. If, as

[6] The Third Circuit correctly characterized Merck's argument as "direct[ing] [the court's] attention away from" the Complete Response Letter, and arguing that informal communications contain a basis for preemption that is "not disclosed" in the Complete Response Letter. *Fosamax*, 852 F.3d at 290, 293 n.135.

Merck contends, FDA had decided that an atypical femoral fracture warning was scientifically unjustified, then FDA would not have extended that invitation. FDA does not, as a matter of practice, toy with regulated parties by inviting them to work with FDA on rejected proposals.[7]

After sending the Complete Response Letter, an FDA official called Merck twice and invited Merck to submit a formal request for a meeting with FDA regarding an atypical femoral fracture warning. Ex. 13, Confoy Decl. Ex. 69; Ex. 15, Ecklund Decl. Ex. 154. Merck assured FDA in a July 2009 letter that such a "meeting request will be submitted," Ex. 16, Ecklund Decl. Ex. 153, but Merck then decided not to do so, Ex. 17, Ecklund Decl. Ex. 119 (Adams Dep. 271:21-272:1), and ceased efforts to warn of femur fractures in the Warnings and Precautions section, *Merck*, 139 S. Ct. at 1674.

Merck unpersuasively suggests (at 27) that FDA's invitation to Merck for further action was limited to the Complete Response Letter. FDA invited further action from Merck on at least four occasions, over several months, in various formats (email, formal letter, telephone call). Thus, "the ball was back in Merck's court to submit a revised, corrected proposal." *Fosamax*, 852 F.3d at 299. Discussions about an atypical femoral fracture warning did not end with FDA rejection, but with Merck's inaction in the face of FDA's repeated pleas for further engagement.

FDA's statements in 2010 further undermine Merck's preemption defense. FDA stated in March 2010 that it was "working closely with outside experts," including the Task Force, "to gather additional information that may provide more insight" into the connection between

[7] Merck relies (at 9, 26) on notes from its employee, Charlotte Merritt, who attributed to an FDA employee the sentiment that "[t]he conflicting nature of the literature d[id] not provide a clear path forward." Ex. 33 at A1971. The Third Circuit correctly recognized the questionable reliability of these double-hearsay notes as evidence of FDA's intentions. *See Fosamax*, 852 F.3d at 291 n.125. Regardless, under federal law, Merck bore responsibility for providing "a clear path forward," as the Task Force would do less than 18 months later. *See Wyeth*, 555 U.S. at 570-71; *infra* p. 30.

bisphosphonates and atypical femoral fractures. Ex. 18 at A1508. That statement shows the FDA persisted after Merck refused to engage with FDA, seeking from outside experts the information it could not get from Merck. The statement that, "[a]t this point, the data that FDA has reviewed have not shown a clear connection" between bisphosphonates and atypical femoral fractures, *id.*, does not signify that FDA prohibited a warning, because the standard for adding a warning is far lower: Merck was permitted (and obligated) to add a warning "as soon as there is reasonable evidence of a causal association with a drug; *a causal relationship need not have been definitely established*." 21 C.F.R. § 201.57(c)(6)(i) (emphasis added).

FDA's statements surrounding the release of the Task Force Report belie Merck's portrayal of the report (at 26) as a "game-changer" that for the first time established a scientific basis for an atypical femoral fracture warning. Rather, FDA explained that the Task Force Report "summarized" "data," Ex. 19 at A1119, and "clarif[ied] the features of atypical femur fractures," Ex. 20 at A1392, thus "help[ing] [FDA] understand these fractures a little bit better," *id.* at A1396. That is precisely what Merck could and should have done years earlier. *See* Ex. 25, Sharfstein Br. 19-20 ("FDA did not view the Task Force Report as providing new data connecting bisphosphonates to atypical femoral fractures but rather a summary of existing data . . . . Merck had access to that same data, and Merck could have assisted FDA in understanding the data, but instead Merck submitted a prior approval supplement that sought to warn about stress fractures instead of the fractures that FDA had been concerned about, AFFs.").

III. When Proposing Its Stress-Fracture Warning, Merck Did Not Fully Inform FDA Of The Justifications For A Warning Of Atypical Femoral Fractures

Merck has not shown that "it fully informed the FDA of the justifications for the warning required by state law." *Merck*, 139 S. Ct. at 1678. To meet its burden, Merck must "demonstrate

that the FDA possessed all the information it deemed necessary" to decide whether to approve an adequate atypical femoral fracture warning. *Avandia*, 945 F.3d at 759.

A. Merck Did Not Fully Inform FDA Of The Justifications For The Warning State Law Required

Merck argues (at 19) that FDA was fully informed because Merck sent the agency a data dump of case reports and articles about femur fractures. But preemption requires informing FDA of the "justifications for the warning required by state law." *Merck*, 139 S. Ct. at 1678; *see Wyeth*, 555 U.S. at 572-73 (no preemption where manufacturer never "supplied the FDA with an evaluation or analysis concerning the specific dangers" at issue). Merck failed to explain properly how the data supported a warning of atypical femoral fractures.

1. Merck's submissions were incomplete and misleading

Far from fully informing FDA of the justifications for an atypical femoral fracture warning, Merck's PAS submission, including its Clinical Overview of the data and literature, Ex. 11 at A2748-59, actively confused the issue by providing misleading information that described atypical femoral fractures inaccurately and conflated them with stress fractures. As Dr. Burr (one of the world's leading orthopedic scientists and principal author of the Task Force Report) explained in an unrebutted expert report, "Merck failed to adequately apprise the FDA of the true nature of the AFF problem in September of 2008 given the data that was available to it at that time." Ex. 3 at A884 (¶ 87). Dr. Burr explained many ways in which Merck's submission was inaccurate or misleading. Merck did not "provide the FDA with any possible pathogenesis for AFF from long-term Fosamax," meaning the scientific mechanism through which Fosamax causes atypical femoral fractures. That was "important in this context" because without it "the FDA . . . might conflate" ordinary osteoporotic fractures Fosamax prevents with atypical femoral

fractures Fosamax causes. *Id.* at A880 (¶¶ 69-70); *see also* Ex. 4, Lane/Vigorita Br. 19 (Merck "omitted any discussion of the pathogenesis of atypical femur fractures").

Compounding the problem, Merck's Clinical Overview misleadingly stated "that fractures with 'similar clinical features' had previously been reported in patients not taking Fosamax," ignoring that atypical femoral fractures suffered by Fosamax users had unique features that were not present in other thigh fractures. Ex. 3 at A881 (¶ 72). Merck thus "improperly" "conflate[d] the occurrence of any subtrochanteric fracture with fractures that have specific features of atypia." *Id.* As Dr. Burr explained, "Merck should have better described this unique fracture to the agency and highlighted that this fracture pattern, particularly in the femoral shaft, was rarely reported prior to the availability of [bisphosphonates]. Instead, Merck appears to have created a submission which suggests that this fracture is much more common in the absence of [bisphosphonates] than it actually is." *Id.* at A882 (¶ 76); *see* Ex. 4, Lane/Vigorita Br. 16 (Merck "failed to convey the unique features of these fractures").[8]

Furthermore, both the Clinical Overview and Merck's proposed warning identified risk factors that "simply were not associated with AFF." Ex. 3 at A883 (¶ 79). By emphasizing these false risk factors, "it appears that Merck was attempting to confound the true nature of the association between Fosamax and AFFs." *Id.* (¶ 81). Relatedly, "[b]y choosing to characterize AFFs as 'stress fractures' in its submission to the FDA, Merck improperly conflated the underlying fracture mechanism that leads to AFFs with the ultimate outcome." *Id.* at 884 (¶ 84).

[8] *See also* Ex. 4, Lane/Vigorita Br. 20 (Merck "improperly suggested there was an established background rate for atypical femur fractures in patients not exposed to Fosamax. This suggestion was not supported by medical evidence, and it erroneously conflated typical fractures seen in the osteoporotic population with so-called Fosamax fractures.").

2. Merck's communications deprived FDA of needed information

FDA statements confirm the agency did not fully understand atypical femoral fractures in 2008 and 2009. FDA needed the additional information that Merck failed to provide.

In June 2008, FDA asked Merck to submit information regarding "all hip and femoral fracture" reports it had received. Ex. 10 at A1145. But "FDA did not seek any information focused specifically on the atypical features seen prominently in patients in the published medical literature. . . . These omissions suggest FDA did not yet fully understand the nature of atypical femur fractures and was in need of a medically accurate education on the subject." Ex. 4, Lane/Vigorita Br. 17. In April 2009, a month before the Complete Response Letter, an FDA official emailed Merck to say the agency wanted to "work with . . . Merck to decide on language for a [Warnings and Precautions] atypical fracture language, if it is warranted." Ex. 12 at A1498. This email indicates that FDA was uncertain about the appropriate warning language and needed more information from Merck "to decide on language."

In the Complete Response Letter itself, FDA stated that "[i]dentification of 'stress fractures' *may not* be clearly related to the atypical subtrochanteric fractures that have been reported in the literature." Add. 2 (emphasis added). The language "may not" confirms that Merck's efforts to conflate stress fractures and atypical femoral fractures left FDA uncertain about the differences between the two types of fractures. In the months following the Complete Response Letter, the FDA repeatedly invited Merck to request a meeting with the FDA to discuss a potential atypical femoral fracture warning, Ex. 13, Confoy Decl. Ex. 69; Ex. 15, Ecklund Decl. Ex. 154; Ex. 14, Ecklund Decl. Ex. 152, but Merck failed to do so. Ex. 17, Ecklund Decl. Ex. 119 (Adams Dep. 271:21-272:1).

Delayed by Merck's inaction, FDA reported several months later that it still needed "to gather additional information that may provide more insight" about the relationship between

bisphosphonates and atypical femoral fractures. Ex. 18 at A1508. The Task Force Report "clarif[ied] the features of atypical femur fractures," Ex. 20 at A1392, "helped [FDA] understand these fractures a little bit better," *id.* at A1396, and prompted FDA to mandate a warning. Merck should have provided that clarification much earlier. As the Supreme Court explained, a drug manufacturer such as Merck "bears responsibility for the content of its label at all times." *Merck*, 139 S. Ct. at 1677. "[W]hen the risks of a particular drug become apparent, the manufacturer has a duty to provide a warning that adequately describe[s] that risk." *Id.*

The history shows that Merck never provided a warning adequately describing the risk of atypical femoral fractures or justifications for such a warning. The company's misleading PAS submission left the FDA uncertain about the nature of atypical femoral fractures. The FDA needed clarification about the features of atypical femoral fractures, and, because Merck rebuffed the FDA's repeated pleas for further engagement, the FDA did not get that clarification until the Task Force Report. Merck never provided "all the information [FDA] deemed necessary" to decide on approval of an adequate atypical femoral fracture warning. *Avandia*, 945 F.3d at 759.

B. Merck Fails To Show That It Fully Informed FDA Of The Risks Of Atypical Femoral Fractures

Merck points to no record evidence showing that FDA was fully informed. Instead, Merck tries to avoid its burden in two ways, neither of which succeeds.

First, Merck argues (at 17) that Judge Pisano concluded that Merck did not "withh[o]ld information" from FDA. But Judge Pisano did not apply the Supreme Court's standard, which requires the manufacturer to demonstrate that it "*fully* informed the FDA of *the justifications* for the warning required by state law." *Merck*, 139 S. Ct. at 1672 (emphases added). A data dump of case reports does not suffice. The court also refused to consider Dr. Burr's highly pertinent report, reasoning that it was "merely expert opinion," Ex. 24 at A28, and that allowing Plaintiffs

to offer expert evidence that Ms. Glynn did not offer at trial "would . . . defeat the efficiency of an MDL," *id.* at A15. Judge Pisano's vacated opinion is not binding, and his refusal to consider evidence such as Dr. Burr's report based on the *Glynn* trial (to which Plaintiffs were not parties) was erroneous. *See Fosamax*, 852 F.3d at 302 ("[T]he District Court's understandable desire to streamline proceedings cannot override the Plaintiffs' basic trial rights.").

Second, Merck erroneously argues (at 20) that Plaintiffs waived the issue. At every stage of briefing – before this Court, the Third Circuit, and the Supreme Court – Plaintiffs consistently argued that Merck's PAS submission was misleading because it did not describe atypical femoral fractures accurately and sought to conflate atypical femoral fractures with stress fractures.[9]

* * *

FDA never "prohibited" Merck from adding an adequate warning of atypical femoral fractures, but merely "rejected Merck's proposal to warn of 'stress fractures.'" *Merck*, 139 S. Ct. at 1674, 1678. Merck never "fully informed the FDA of the justifications for" an adequate atypical femoral fracture warning. *Id.* at 1678. Therefore, Plaintiffs' claims are not preempted.

CONCLUSION

The Court should hold that federal law does not preempt Plaintiffs' claims.

---

[9] *See* Fact Br. 60 ("Merck's September 15, 2008 PAS submission to the FDA and the 'Clinical Overview' document was deficient and failed to inform the FDA of the true nature of the risk of low-energy femur fracture based on what was known (or knowable) to Merck."); Pls.' Warnings & Precautions Failure-To-Warn Br. 24, MDL DN 2995-4 (Sept. 30, 2013) ("Merck's federal preemption defense fails because the PAS it submitted to the FDA misstated the relevant risk of injury suffered by Plaintiffs."); Ex. 34, Pls.' Third Cir. Br. 59-61 (Merck's PAS was "misleading" because of conflation of stress fractures and AFFs); *id.* at 60 n.24 (quoting Dr. Burr's criticisms of Clinical Overview); Ex. 35, Pls.' Cert. Opp. 19 (Merck's PAS contained "inaccurate and misleading conflation of atypical femoral fractures with stress fractures"); Ex. 36, Pls.' Merits Br. 37 (Merck's PAS "contained a clinical overview that obscured the nature of atypical femoral fractures"); Ex. 37, Pls.' Third Cir. Letter Br. 9 ("Merck could have obtained a decision from FDA approving a warning about AFFs in 2009 or earlier" had it not "obfuscated the true nature of AFFs by focusing its [Prior Approval Supplement] on stress fractures").

Dated: May 6, 2020

Respectfully submitted,

CARELLA, BYRNE, CECCHI, OLSTEIN, BRODY & AGNELLO
5 Becker Farm Road
Roseland, NJ 07068
Plaintiffs' Co-Liaison Counsel

/s/ James E. Cecchi
James E. Cecchi

Christopher A. Seeger
David R. Buchanan
SEEGER WEISS LLP
55 Challenger Road
Ridgefield Park, NJ 07660
Plaintiffs' Co-Liaison Counsel

Paul J. Pennock
Ellen Relkin
WEITZ & LUXENBERG
700 Broadway
New York, NY 10003

Timothy M. O'Brien
Brandon L. Bogle
LEVIN, PAPANTONIO, THOMAS, MITCHELL, RAFFERTY & PROCTOR, P.A.
316 South Baylen Street, 6th Floor
Pensacola, FL 32502

David C. Frederick (*pro hac vice pending*)
Brendan J. Crimmins (*pro hac vice pending*)
Jeremy S.B. Newman (*pro hac vice pending*)
KELLOGG, HANSEN, TODD, FIGEL & FREDERICK, P.L.L.C.
1615 M Street, N.W., Suite 400
Washington, D.C. 20036

ADDENDUM

TABLE OF CONTENTS

Page

Excerpt of Merck's 2008 Prior Approval Supplement Application (Ex. 38, A1371)

Low-Energy Femoral Shaft Fracture

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

limited access

Restricted Confidential

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-560/S-054, NDA 21-575/S-015, NDA 21-762/S-008

COMPLETE RESPONSE

James H. Adams
MAY 22 2008

Merck & Co., Inc.
Attention: James Adams, M.S.
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065-0900

Dear Mr. Adams

Please refer to your supplemental new drug applications (sNDAs) dated September 15, 2008, received September 15, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

FOSAMAX (alendronate sodium) Tablets (NDA 20-560/S-054)
FOSAMAX (alendronate sodium) Oral Solution (NDA 21-575/S-015)
FOSAMAX Plus D (alendronate sodium/cholecalciferol) Tablets (NDA 21-762/S-008)

We acknowledge receipt of your amendments for FOSAMAX Tablets and FOSAMAX Oral Solution, both dated September 19, 2008.

These supplemental new drug applications propose adding language to the **PRECAUTIONS** section and the **ADVERSE REACTIONS, Post-Marketing Experience** subsection of the Package Inserts (PIs) to describe low-energy fractures at the subtrochanteric region of the femoral shaft. In addition these supplements propose adding language describing this type of fracture in the Patient Package Inserts (PPIs).

We have completed the review of your applications, as amended, and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and our recommendation to address this issue.

1. While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the FOSAMAX Tablets and Oral Solution and FOSAMAX Plus D Tablets labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress

fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

2. We recommend that you add "low energy femoral shaft and subtrochanteric fractures" in the **ADVERSE REACTIONS, Post-Marketing Experience** subsection of the respective package inserts.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change before approval of these supplemental applications.

If you have any questions, call Karl Stiller, Regulatory Project Manager, at (301) 796-1993.

Sincerely,

(See appended electronic signature page)

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Scott Monroe
5/22/2009 11:06:15 AM

Excerpt of Jan. 2011 Fosamax label (Ex. 1, A1070-71)

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

No. 17-290

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Writ of Certiorari to
the United States Court of Appeals
for the Third Circuit

BRIEF OF *AMICI CURIAE* JOSEPH LANE, M.D., AND VINCENT VIGORITA, M.D., IN SUPPORT OF RESPONDENTS

KAREN BARTH MENZIES
COUNSEL OF RECORD
ANDRE M. MURA
GIBBS LAW GROUP LLP
505 14TH STREET, SUITE 1110
OAKLAND, CA 94612
(510) 350-9700
kbm@classlawgroup.com

Counsel for Amici Curiae

November 21, 2018

X-rays of stress fractures and atypical femur fractures illustrate these differences. Look first at an image of a stress fracture in a femur:[12]

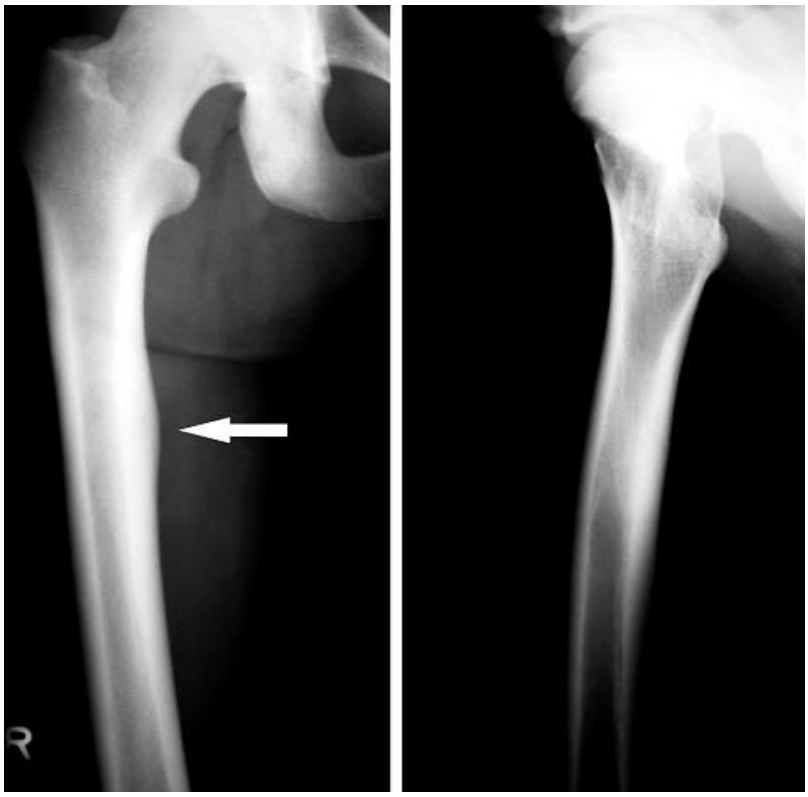

Figure 1 Anteroposterior and lateral roentgenograms showing stress fractures in the proximal third of the right femoral shaft (white arrow).

failed to heal due to Fosamax. (JA385, 396 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*).

[12] Ivkovic, *Stress Fractures of the Femoral Shaft in Athletes: a New Treatment Algorithm*, 40 BR J SPORTS MED 518-520 (2006), at fig. 1.

Look next at radiographs of atypical femur fractures in three patients:[13]

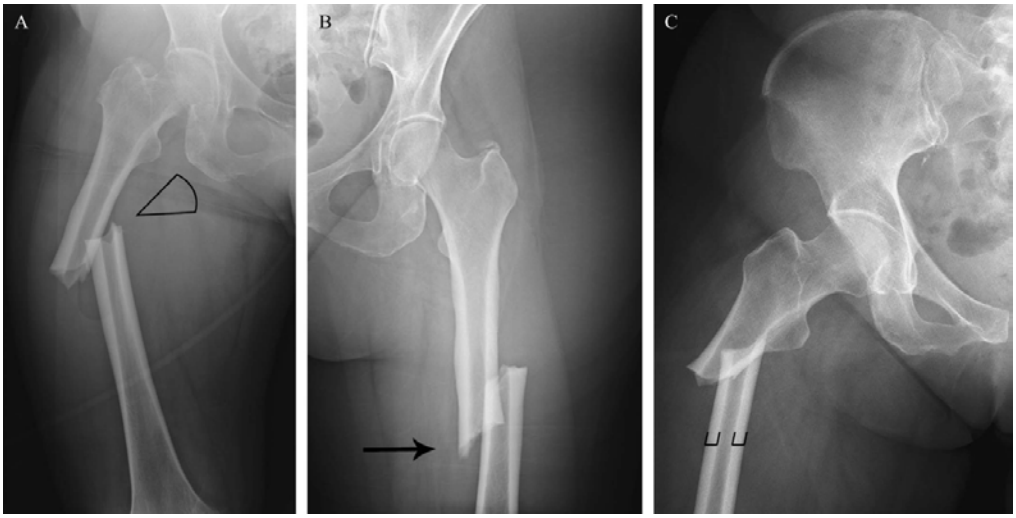

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

In this second set of images, a fracture pattern runs across the bone, and—atypically—involves a thickening (hypertrophy) rather than a thinning of the cortical bone by the fracture sites. JA661-663 (Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use*); JA385, 387-89 396 (Lenart, *Atypical*

[13] Neviaser, *Low-Energy Femoral Shaft Fractures Associated with Alendronate Use,* 22 J ORTHOP TRAUMA 346-50, at fig. 1 (May/June 2008).

CERTIFICATE OF SERVICE

I hereby certify that, on May 6, 2020, a copy of the foregoing was served on the following, counsel for Defendant:

Karen A. Confoy
FOX ROTHSCHILD LLP
Princeton Pike Corporate Center
997 Lenox Drive
Lawrenceville, NJ 08648
Tel: (609) 844-3033
Fax: (609) 896-1469
kconfoy@foxrothschild.com

Stephen E. Marshall
VENABLE LLP
750 E. Pratt Street
Suite 900
Baltimore, MD 21202
Tel: (410) 244-7407
Fax: (410) 244-7742
semarshall@venable.com

Shay Dvoretzky
Yaakov M. Roth
Jeffrey R. Johnson
JONES DAY
51 Louisiana Avenue NW
Washington, DC 20001
Tel: (202) 879-3939
Fax: (202) 782-8585
sdvoretzky@jonesday.com
yroth@jonesday.com
jeffreyjohnson@jonesday.com

Attorneys for Defendant
Merck Sharp & Dohme Corp.

/s/ James E. Cecchi
James E. Cecchi